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Reaction of CH-Acidic Phosphorylated Acetamidines with Chlorotrimethylsilane

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Abstract—A reaction of sodium derivatives of C-phosphorylated acetamidines with clorotrimethylsilane was investigated. The reaction proceeds selectively with the formation of the acetamidines silylated derivatives. Using the CH-acid properties of C-phosphorylated acetamidines a convenient method was developed for the synthesis of a new type of organophosphorus-silicon amidines.

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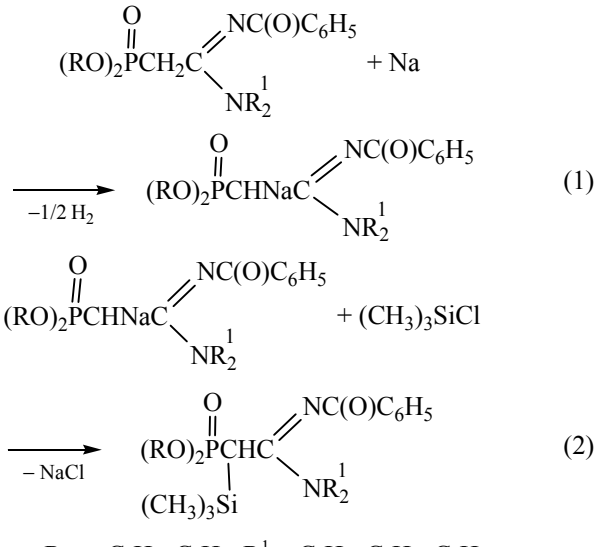
Organophosphorus amidines are of practical interest due to the possibility of their use in various branches of economics like agriculture and medicine [1]. This work is a continuation of investigations of the reactions of amidines based on the use of the CH-acid properties of activated methylene group in these compounds [2, 3]. In order to synthesize new structures of amidines extending the range of application of these compounds the silylation was carried out of the C-phosphorylated acetamidine sodium derivatives with chlorotrimethylsilane. These reactions are expressed by the Eqs. (1) and (2).



(1)

(2)

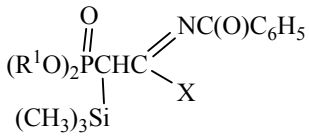
R = *i*-C_3H_7, C_4H_9; R^1 = C_2H_5, C_3H_7, C_4H_9.

The initial sodium derivatives were prepared by the action of metallic sodium on the C-phosphorylated acetamidines in the dioxane medium. Reaction (1) was carried out at heating to 40–50°C with vigorous stirring until complete conversion of sodium. Since the yield of the sodium derivative is close to quantitative, the second stage of the process, silylation [reaction (2)], was carried out without isolation of the sodium derivative. To the reaction mixture obtained was added dropwise while stirring a calculated amount of chlorotrimethylsilane in dioxane at 20–30°C. To complete the silylation, the temperature was raised to 50°C and the mixture was stirred for 3 h. The sodium : P-phosphorylated acetamidine : chlorotrimethylsilane molar ratio was 1:1:(1–1.1). To isolate the target substance, the reaction mixture was cooled to a temperature of 20–30°C, sodium chloride was filtered off, and the solvent was removed by distillation in a vacuum. The chemically pure target product was obtained by purification by adsorption column chromatography on silica gel of μLC 5/40 grade. The composition and structure of the synthesized compounds was established from elemental analysis, molecular refraction, ^{1}H NMR and IR spectroscopy. The yield of the reaction products was 82–87%.

Physicochemical properties of compounds **IV** are listed in Table 1.

The synthesized compound are viscous pale-orange liquids, readily soluble in organic solvents (dioxane, acetone) and poorly soluble in water.

Physico-chemical properties of silylated acetamidines



Comp. no.	R^1	X	Yield, %	n_D^{20}	d_4^{20}	MR_D		Found, %		Formula	Calculated, %	
						found	calculated	N	P		N	P
I	C_4H_9	$N(C_4H_9)_2$	82	1.4775	1.0080	153.24	152.99	5.33	5.59	$C_{28}H_{41}N_2O_4PSi$	5.19	5.75
II	*i*-C_3H_7	$N(C_3H_7)_2$	86	1.4517	1.0017	137.12	136.53	6.30	7.19	$C_{20}H_{43}N_2O_4PSi$	6.17	6.83
III	C_4H_9	$N(C_2H_5)_2$	85	1.4881	1.0060	137.11	136.49	5.64	7.19	$C_{23}H_{43}N_2O_4PSi$	5.81	6.43
IV	*i*-C_3H_7	$N(C_2H_5)_2$	86	1.4685	1.0326	130.61	129.83	6.45	6.38	$C_{22}H_{39}N_2O_4PSi$	6.39	7.08
V	*i*-C_3H_7	$N(CH_2CH_2)_2O$	87	1.4965	1.0409	133.54	132.75	6.31	6.35	$C_{28}H_{40}N_2O_5PSi$	6.19	6.864

We performed computer screening for biological activity using PASS program of the Orekhovich Institute of Biomedical Chemistry, Russian Academy of Medical Sciences. According to the results obtained, in the silylated acetamidines various types of activitiy were revealed: antitumor, anti-inflammatory, fungicidal, and a possibility of using them as a uterine relaxant.

EXPERIMENTAL

***N,N*-Dibutyl-*N*'-benzoyl(trimethylsilyl)(dibutoxyphosphoryl)acetamidine (I).** To a solution of 2 g (0.0043 mol) of *N,N*-dibutyl-*N*'-benzoyl(dibutoxyphosphoryl)acetamidine in 4 ml of anhydrous dioxane at 20–30°C was added in small portions while stirring 0.1 g (0.0043 mol) of sodium. The reaction mixture was stirred until complete conversion of sodium. To the solution of the resulting acetamidine sodium derivative was added dropwise 0.34 g (0.0047 mol) of chlorotrimethylsilane in 2 ml of dioxane at 20–30°C while stirring. The molar ratio of *N,N*-dibutyl-*N*'-benzoyl(dibutoxyphosphoryl)acetamidine : sodium : chlorotrimethylsilane = 1: 1: 1.1. The temperature of the reaction mixture was raised to 50°C and stirring was continued for 3 h. Sodium chloride formed was separated by filtration, the solvent was removed by distillation in vacuo (at 15–20 hPa), and the residue was evacuated for 1 h at 2–4 hPa at 50°C. Yield 1.9 g (82%). The purification was performed by adsorption column chromatography on silica gel of μLC 5/40 grade. ^{1}H NMR spectrum (CCl_4), δ, ppm: 0 s (9H, CH_3Si) 0.75 m (12H, CH_3), 1.21 m (16H, CH_2), 2.77 d (1H, CHP) to 3.47 (4H, NCH_2), 3.68 m (4H, CH_2O), 7.18 m (5H, C_6H_5). IR spectrum, ν, cm^{-1}: 748, 856–892 (C–Si); 982–1066 (POC), 1222 (P=O), 1610 (C⋯C); 1654 (C=N); 1720 (C=O).

***N,N*-dipropyl-*N*'-benzoyl(trimethylsilyl)(diisopropoxyphosphoryl)acetamidine (II)** was synthesized similarly from 2 g (0.0048 mol) of *N,N*-dipropyl-*N*'-benzoyl(diisopropoxyphosphoryl)acetamidine, 0.11 g (0.0048 mol) of sodium and 0.53 g (0.0052 mol) of chlorotrimethylsilane. The molar ratio of *N,N*-dipropyl-*N*'-benzoyl(diisopropoxyphosphoryl)acetamidine : sodium : chlorotrimethylsilane = 1: 1: 1.08. Yield 1.6 g (86%). ^{1}H NMR spectrum (CCl_4), δ, ppm: 0 s (9H, CH_3Si), 0.94 d (12H, CH_3), 1.3 m (6H, CH_3), 1.1 m (4H, CH_2), 2.77 d (1H, CHP), 3.46 t (4H, NCH_2) 3.97 m (2H, CH_2OR) 7.25 m (5H, C_6H_5). IR spectrum, ν, cm^{-1}: 784, 838–856 (C–Si); 964–1030 (POC), 1228 (P=O), 1600 (C⋯C); 1654 (C=N); 1720 (C=O).

***N,N*-Diethyl-*N*'-benzoyl(trimethylsilyl)(dibutoxyphosphoryl)acetamidine (III)** was synthesized similarly from 1.60 g (0.0039 mol) of *N,N*-diethyl-*N*'-benzoyl(dibutoxyphosphoryl)acetamidine, 0.09 g (0.0039 mol) of sodium and 0.42 g (0.0039 mol) of chlorotrimethylsilane. The molar ratio of *N,N*-diethyl-*N*'-benzoyl(dibutoxyphosphoryl)acetamidine : sodium : chlorotrimethylsilane = 1: 1: 1. Yield 1.6 g (85%).

^{1}H NMR spectrum (CCl_4), δ, ppm: 0 s (9H, CH_3Si), 1.4 t (12H, CH_3), 1.37 m (8H, CH_2), 2.77 d (1H, CHP) 3.55 q (4H, NCH_2), 3.89 m (4H, CH_2OR) 7.33 m (5H, C_6H_5). IR spectrum, ν, cm^{-1}: 784, 832–844 (C–Si); 1030–1066 (POC), 1233 (P=O), 1590 (C⋯C); 1654 (C=N); 1720 (C=O).

***N,N*-Diethyl-*N*'-benzoyl(trimethylsilyl)(diisopropoxyphosphoryl)acetamidine (IV)** was synthesized similarly from 1.40 g (0.0037 mol) of *N,N*-diethyl-*N*'-benzoyl(diizopropoxyphosphoryl)acetamidine, 0.084 g (0.0037 mol) of sodium and 0.42 g (0.0038 mol) of

chlorotrimethylsilane. The molar ratio *N,N*-diethyl-*N*'-benzoyl(diizopropoxyphosphoryl)acetamidine : sodium : chlorotrimethylsilane=1: 1: 1.05. Yield 1.5 g (86%). ^{1}H NMR spectrum (CCl_4), δ, ppm: 0 s (9H, CH_3Si), 0.93 d (12H, CH_3), 5.1 t (6H, CH_3), 1.27 m (16N, CH_2), 2.77 d (1H, CHP) 3.23 q (4H, NCH_2) 4.65 m (2H, CHOP) 7.30 m (5H, C_6H_5). IR spectrum, ν, cm^{-1}: 790, 820–838 (C–Si); 988–1030 (POC), 1228 (P=O), 1654 (C=N); 1720 (C=O), 1594 (C⋯C).

***N*-Morpholino-*N*'-benzoyl(trimethylsilyl)(diisopropoxyphosphoryl)acetamidine (V)** was synthesized similarly from 1.70 g (0.0043 mol) of *N*-morpholino-*N*'-benzoyl(diisopropoxyphosphoryl)acetamidine, 0.099 g (0.0043 mol) of sodium and 0.48 g (0.0046 mol) of chlorotrimethylsilane. The molar ratio *N,N*-diethyl-*N*'-benzoyl(diizopropoxyphosphoryl)acetamidine : sodium : chlorotrimethylsilane=1: 1: 1.07. Yield 1.9 g (87%). ^{1}H NMR spectrum (CCl_4), δ, ppm: 0 s (9H, CH_3Si) 1.07 d (12H, CH_3), 2.73 d (1H, CHP), 3.23 t (4H, NCH_2) 3.57 t (4H, CH_2O), 4.67 m (2H, POCNO) 7.29 m (5H, C_6H_5); IR spectrum, ν, cm^{-1}: 760, 838–856 (C–Si); 980–1030 (POC), 1230 (P=O), 1666 (C=N); 1720 (C=O), 1594 (C⋯C).

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